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PATENT

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2/20/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Antonio Lopez CABRERA et al.

Serial No.: 09/660,022 Group No.:

Filed: September 12, 2000 Examiner:

For: SOLID ORAL PHARMACEUTICAL FORMULATION OF MODIFIED RELEASE THAT CONTAINS AN ACID LABILE BENZIMIDAZOLE COMPOUND

Attorney Docket: U 012473-1

Assistant Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

We draw the attention of the Examiner to the references listed on the attached Form PTO-1449.

We also draw the Examiner's attention to the attached comments which have been provided by applicant's foreign agent.

Patent application PCT **WO98/53803** (ASTRA) studies the effect of the nature of the hydroxypropyl methylcellulose (HPMC) on the release of omeprazole in a oral pharmaceutical formulation with enteric omeprazole coating and proposes the use of a low-viscosity HPMC, of a certain quality grade (with a certain cloud point) in the manufacture of an oral pharmaceutical formulation with enteric coating that contains, as an active ingredient, a compound selected from the group formed by omeprazole, an alkaline salt of omeprazole, the (-) enantiomer of

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CERTIFICATE OF MAILING (37 CFR 1.8a)

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Janet I. Cord
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Practitioner's Docket No. U 012473-1

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TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT WITHIN THREE MONTHS OF FILING OR BEFORE MAILING OF FIRST OFFICE ACTION (37 C.F.R. 1.97(b))

NOTE: "An information disclosure statement shall be considered by the Office if filed by the applicant: (1) within three months of the filing date of a national application; (2) within three months of the date of entry of the national stage as set forth in § 1.491 in an international application; or (3) before the mailing date of a first Office action on the merits, whichever event occurs last." 37 C.F.R. 1.97(b).

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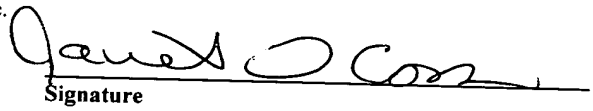

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*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

NOTE: The "filing date of a national application" under 37 C.F.R. 1.97(b) has two possible meanings. Where the filing is a direct one to the United States Patent & Trademark office, the filing is defined in 37 C.F.R. 1.53(b) as "the date on which: (1) A specification containing a description pursuant to § 1.71 and at least one claim pursuant to § 1.75; and (2) any drawing required by § 1.81(a), are filed in the Patent and Trademark Office in the name of the actual inventor or inventors as required by § 1.41." 37 C.F.R. 1.97(b)(1). On the other hand, an international application that enters the national stage occurs when the applicant has filed the documents and

fees required by 35 U.S.C. § 371(c) within the periods set forth in § 1.494 or § 1.495. 35 U.S.C. § 371(c) requires the filing of the following: (1) the national fee; (2) a copy of the international application, unless already sent by the International Bureau, and an English translation if filed in another language; (3) amendments under PCT Article 19, with a translation into English if made in another language; (4) an oath or declaration; and (5) a translation into English of any annexes to the international preliminary examination report, if such annexes were made in another language. 37 C.F.R. 1.97(b)(2).

IDENTIFICATION OF TIME OF FILING THE ACCOMPANYING INFORMATION DISCLOSURE STATEMENT

The information disclosure statement submitted herewith is being filed within three months of the filing date of the application or date of entry into the national stage of an international application or before the mailing date of a first Office action on the merits, whichever event occurs last. 37 C.F.R. 1.97(b).

NOTE: "No certification or fee is due when the filing is made within the above time period. It is advisable to ensure that no Office action has been mailed if the disclosure statement is delayed until after three months from filing."

NOTE: "An information disclosure statement will be considered to have been filed on the day it was received in the Office, or on an earlier date of a mailing if accompanied by a properly executed certificate of mailing under 37 C.F.R. 1.8, or Express Mail certificate under 37 C.F.R. 1.10. An office action is mailed on the date indicated in the Office action." Notice of April 20, 1992 (1138 O.G. 37-41, 39).

NOTE: "The term 'national application' includes continuing applications (continuations, divisions, continuations-in-part) so three-months will be measured from the actual filing date of an application as opposed [sic] to the effective date of a continuing application." Notice of April 20, 1992 (1138 O.G. 37-41, 39).

NOTE: "An action on the merits means an action which treats the patentability of the claims in an application, as opposed to only formal or procedural requirements. An action on the merits would, for example, contain a rejection or indication of allowability of a claim or claims rather than just a restriction requirements (37 C.F.R. 1.142) or just a requirement for additional fees to have a claim considered (37 C.F.R. 1.16(d)). Thus, if an application was filed on Jan. 1 and the first Office action on the merits was not mailed until six months later on July 1, the examiner would be required to consider any proper information disclosure statement filed prior to July 1." Notice of April 20, 1992 (1138 O.G. 37-41, 39).

***WARNING:** "A petition for suspension of action to allow applicant time to submit an information disclosure statement will be denied as failing to present good and sufficient reasons, since 37 C.F.R. 1.97 provides adequate recourse for the timely submission of prior art for consideration by the examiner." Notice of July 6, 1992 (1141 O.G. 63).*

SIGNATURE OF PRACTITIONER

Reg. No. 33,778

Tel. No.: (212) 708-1935

Customer No.:

Janet I. Cord
(type or print name of practitioner)

c/o LADAS & PARRY
P.O. Address
26 WEST 61st STREET
NEW YORK, N.Y. 10023

omeprazole and an alkaline salt of the (-) enantiomer of omeprazole, whose formulation comprises (i) a nucleus which contains the active ingredient and optionally a compound of agents) and over said active nucleus (ii) an enteric coating layer which contains said low viscosity HMPC and (iii) an enteric coating layer . The formulation described in this patent application is different from that claimed in this patent application because, among other things, it is not a formulation for modified release and the pellets are different (the pellets that contain one or more intermediate layers formed from an inert non-alkaline water-soluble polymer and from another inert non-alkaline water-insoluble polymer, in which the variation of relative proportions between the two polymers may modulate the rate of liberation of the active ingredient, are not exemplified).

The patent application PCT **WO00/27366** (ASTRAZENECA) studies the effect of the nature of hydroxypropyl cellulose (HPC) on the release of omeprazole in an oral pharmaceutical formulation with enteric coating of omeprazole and proposes the use of an HPC of a certain quality (in particular, with a certain cloud point), in the manufacture of an oral pharmaceutical formulation with enteric coating that contains, as an active ingredient, a compound selected from the group formed by omeprazole, an alkaline salt of omeprazole, one of the pure enantiomers of omeprazole and an alkaline salt of one of the pure enantiomers of omeprazole, whose formulation comprises (i) a nucleus that contains the active ingredient and optionally a compound of alkaline reaction, along with one or more excipients (binding agents, fillers and/or disintegrating agents) and, over said active nucleus (ii) a separating layer that comprises said HPC of certain quality and (iii) an enteric coating layer. The formulation described in this patent application is different from that claimed in the LDE patent application because, among other things, it is not a formulation for modified release and the pellets are different (the pellets that contain one or more intermediate layers formed from an inert non-alkaline water-soluble polymer and from another inert non-alkaline water-insoluble polymer, in which the variation of relative proportions between the two polymers may modulate the rate of liberation of the active ingredient, are not exemplified). This patent application was published on a date (18.05.00) after the priority claimed in this patent application (13.09.99).

U.S. patent **US 6,077,541** (ANDRX) studies the possibility of simplifying the procedure for the preparation of enterically coated omeprazole pellets and proposes a omeprazole dosing form consisting of a capsule that contains some pellets consisting of (i) an inert nucleus, (ii) an active layer that surrounds said inert nucleus constituting the active ingredient, a surfactant, a

filler, a pharmaceutically acceptable alkaline agent and a binding agent, and (iii) a coating layer that surrounds said active layer that consists essentially of an enteric coating agent and an aid for inert processing, in which the coating layer is applied directly over the active layer without prior application of an intermediate separation layer between the active nucleus and the enteric coating. The resulting formulation does not contains an intermediate separation layer, it is stable and bioequivalent with other omeprazole formulations that contain an intermediate layer of separation between the active ingredient and the enteric coating. The formulation described in this patent is different from that claimed in the LDE patent application in that, among other things, it is not a modified release formulation and the pellets are different (protection of omeprazole through the creation of an alkaline environment, absence of intermediate modified release layer(s)).

The patent application PCT **WO00/12064** (ANDRX) studies the possibility of simplifying the procedure for the preparation of enterically coated pellets of omeprazole. It proposes the use of lysine or arginine as a pH stabilising agent and provides a stable pharmaceutical composition of omeprazole for its oral administration that essentially consists of (a) a nucleus of omeprazole or a pharmaceutically salt thereof, a filler and an alkaline agent selected from between lysine and arginine, and (b) a single coating layer over said nucleus that comprises a layer of an enteric coating agent applied through the use of a system based on an organic solvent. The resulting formulation does not contain an intermediate separation layer between the active nucleus and the enteric coating, it is stable and bioequivalent with other omeprazole formulations that contain an intermediate separating layer between the active ingredient and the enteric coating. The formulation described in this patent application is different from that claimed in the patent application LDE in that, among other things, it is not a formulation for modified release and the pellets are different (protection of omeprazole through the creation of an alkaline environment due to the action of lysine or arginine, absence of intermediate layer(s) of modified release). This patent application was published on a date (09.03.00) after that of the priority claimed in this patent application (13.09.99).

The European patent application **EP 0 960 620 A1** (RANBAXY) addresses the problem of developing a stable oral pharmaceutical composition of a pyridylsulphinyl benzimidazole derivative free of alkaline compounds and provides a solution that comprises the use of a vinylpyrrolidone polymer as a stabilising excipient of the benzimidazole compound and so the resulting composition does not require the use of any alkaline agent to prevent the degradation of the active ingredient. The specific compositions exemplified in this patent application differ

from the pharmaceutical formulation of this patent application in that, among other things, they are not modified release tablets nor are they formed from pellets consisting of a mixed inert nucleus, or coated nucleus, with the active ingredient. This patent application was published on a date (01.12.99) after the priority claimed in this patent application (13.09.99).

U.S. patent **US 5,817,338** (ASTRA) addresses the problem of provided tablets that comprise units arranged in the form of enterically coated layers that contain omeprazole that may be manufactured without the compression process significantly affecting the properties of the enteric coating. The solution provided consists of a tablet dosing form of multiple units that contain at least one excipient for tablets and a set of pellets that contain an active ingredient selected from among omeprazole, an alkaline salt of omeprazole, one of the pure enantiomers of omeprazole and an alkaline salt of one of the pure enantiomers of omeprazole, each pellet being coated with at least a layer of enteric coating that comprises a plasticiser agent in a quantity lying between 20 and 50 % by weight with respect to the enteric coating layer with the aim of minimising the reduction in resistance to acids of the units, enterically coated, arranged in layers, after compression to obtain the tablet. The pharmaceutically formulation claimed in this patent application differs from the pharmaceutical compositions exemplified in this patent in that, among other things, the intermediate layer present in the pellets does not contain a mixture of inert non-alkaline water-soluble polymer and another inert non-alkaline water-insoluble polymer, in which the variation of the relative proportions between the two polymers may modulate the rate of release of the active ingredient. Assuming that this patent addresses the same technical problem as that of the present patent application (taking into account that fact that the dosing forms of the multiple units are used for controlled release formulations) it can be affirmed that the solution provided in both cases is different and that this patent (although in column 6, lines 1-17, it states that each separating layer may include ethyl cellulose (EC) and HPMC and mixtures thereof) does not even mention that the mixture of an inert non-alkaline water-soluble polymer and another inert non-alkaline water-insoluble polymer, in one or more intermediate separation layers, may be responsible for the controlled release active ingredient, or that varying the relative proportions of the two polymers the release rate of the active ingredient may be modulated.

U.S. patent **US 4,786,505** (AB HASSLE) addresses the problem of provided stable oral pharmaceutical preparations of omeprazole and the solution that is proposed is an oral pharmaceutical preparation that comprises (i) a nucleus that comprises an active ingredient

selected from omeprazole and a compound of alkaline reaction, an alkaline salt of omeprazole and a compound of alkaline reaction, and an alkaline salt of omeprazole (alone), (ii) an inert coating that is soluble in water or that disintegrates quickly in water and comprises one or more layers of materials selected from among excipients for compression and film-forming compounds, and (iii) an external layer that contains an enteric coating. The pharmaceutical formulation claimed in this patent application differs from the pharmaceutical compositions exemplified in this patent in that, among other things, the intermediate layer present in the pellets does not contain a mixture of an inert non-alkaline water-soluble polymer and another inert non-alkaline water-insoluble polymer, in which the variation of the relative proportions between both polymers may modulate the rate of liberation of the active ingredient.

The patent application PCT **WO98/52564** (CIPLA) addresses the problem of providing stable oral pharmaceutical preparations of benzimidazole and the solution that is put forward is based on the use of a moisture-resistant coating that surrounds the nucleus that contains the active ingredient, said moisture-resistant coating containing at least a hydrophobic material, for example, a polyalkylsiloxane, castor oil, mineral oil, isopropyl miristate, stearic acid, ketyl alcohol or similar, optionally together with a binding agent that may be a hydrophobic or hydrophilic material. In Example 23 (page 18) a formulation is described comprises polyvinylpyrrolidone (PVP) and HPMC; however, in said composition, the mixture formed by PVP and HPMC does not form part of an intermediate layer that surrounds the nucleus or an active layer. This patent application does not mention or suggest that the pellets contain one or more intermediate layers formed by an inert non-alkaline water-soluble polymer and another inert non-alkaline water-insoluble polymer, in which the variation of relative proportions between both polymers can modulate the rate of release of the active ingredient.

The patent application PCT **WO99/48498** (GEA) addresses the problem of providing new stable oral pharmaceutical formulations of derivatives of benzimidazole and the solution that is proposed is based on the incorporation of the active ingredient without using water or an organic solvent, through the use of the fused coating technique to provide preformed nuclei, such as inert nuclei, with a coating layer that comprises an active ingredient, a disintegrating agent and a surfactant in a matrix of a fused coating substance that essentially consists of one or more glycerol and fatty acid esters. The pharmaceutical formulation provided by this patent application includes an intermediate layer, between the internal layer that contains the active ingredient and the external layer that contains an enteric coating, suitable for protecting the active

ingredient from degradation by the ingredients of the enteric coating, that contains, for example, HMPC, HPC or PVP, along with, optionally, a layer of a fused coating substance constituted essentially of one or more glycerol and fatty acid esters, and, optionally, auxiliary agents. This patent application was published on a date (30.09.99) after the priority claimed in this patent application (13.09.99).

Respectfully Submitted,

JANET I. CORD
LADAS AND PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023
REG. NO: 33,778 (212) 708-1935